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(19) **United States**(12) **Patent Application Publication****Sallberg et al.**(10) **Pub. No.: US 2002/0155124 A1**(43) **Pub. Date: Oct. 24, 2002**(54) **VACCINES CONTAINING RIBAVIRIN AND METHODS OF USE THEREOF**

(60) Provisional application No. 60/229,175, filed on Aug. 29, 2000.

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NEWPORT BEACH, CA 92660 (US)**(21) Appl. No.: **10/104,966**(57) **ABSTRACT**(22) Filed: **Mar. 22, 2002****Related U.S. Application Data**

(63) Continuation of application No. 09/705,547, filed on Nov. 3, 2000, now abandoned.

The present invention relates to compositions and methods for enhancing the effect of vaccines in animals, such as domestic, sport, or pet species, and humans. More particularly, the use of Ribavirin as an adjuvant to a vaccine protocol and compositions having Ribavirin and an antigen are described.

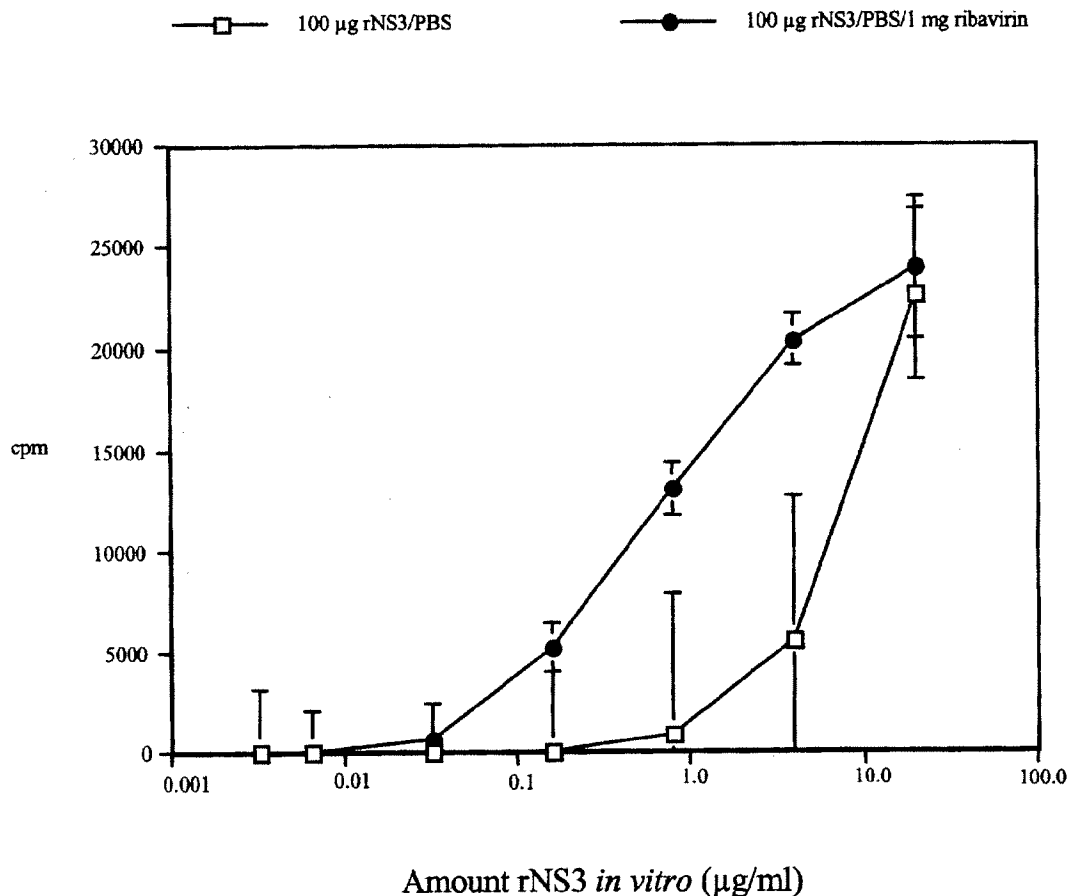


FIGURE 1

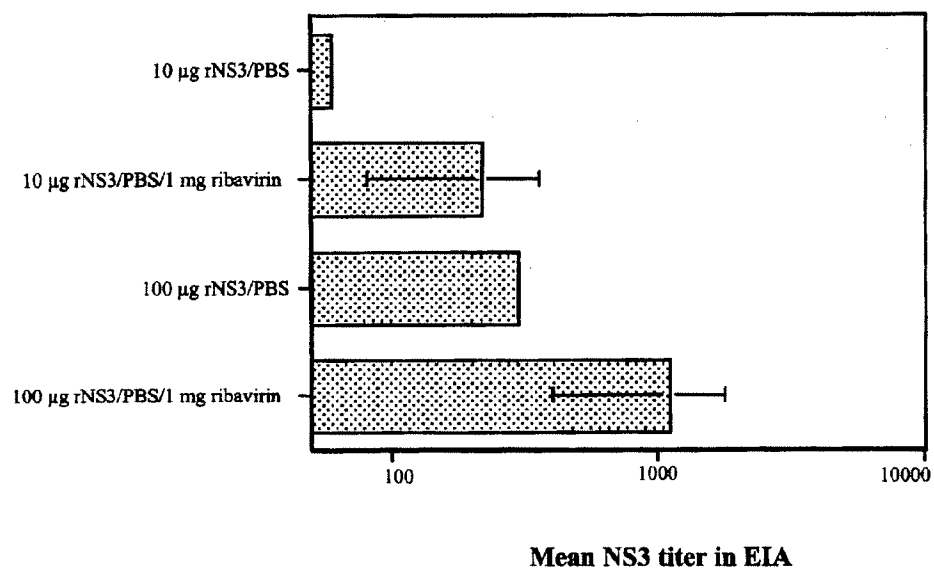


FIGURE 2

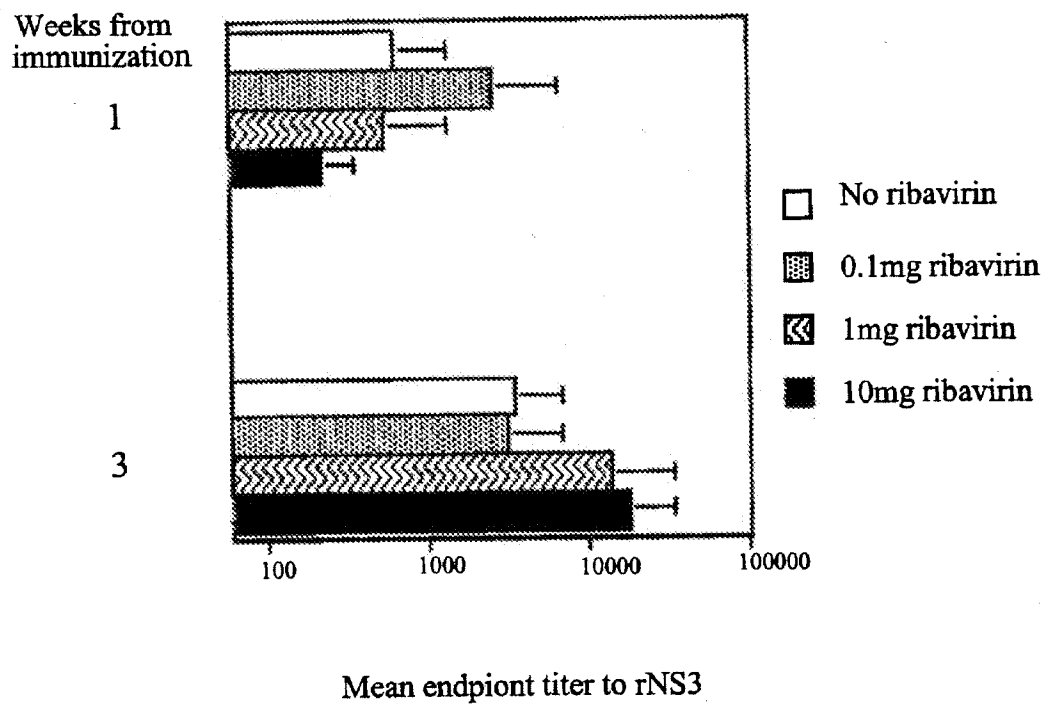
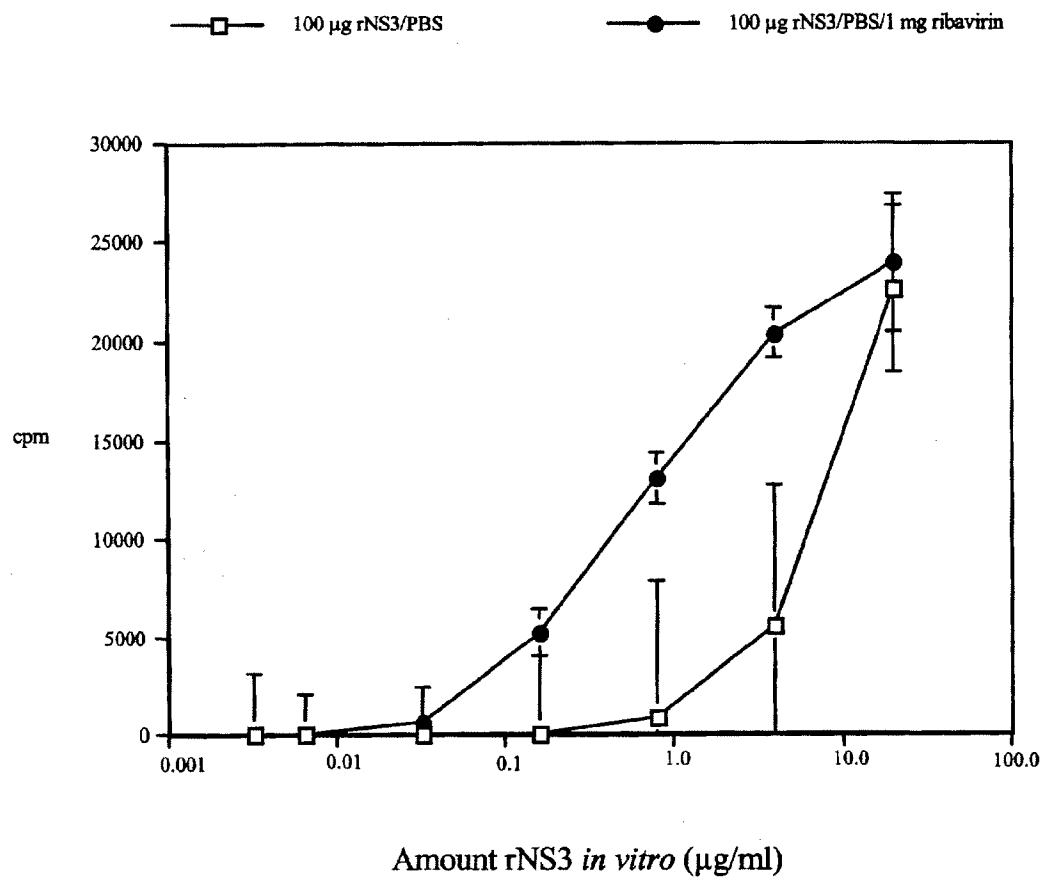


FIGURE 3



VACCINES CONTAINING RIBAVIRIN AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. application Ser. No. 09/705,547 having a filing date of Nov. 3, 2000, which claims the benefit of priority of U.S. provisional patent application No. 60/229,175, filed Aug. 29, 2000; both of which are hereby expressly incorporated by reference in their entireties.

FIELD OF THE INVENTION

[0002] The present invention relates to compositions and methods for enhancing the effect of vaccines in animals, such as domestic, sport, or pet species, and humans. More particularly, preferred embodiments concern the use of Ribavirin as an adjuvant and compositions having Ribavirin and an antigen.

BACKGROUND OF THE INVENTION

[0003] The use of vaccines to prevent disease in humans, farm livestock, sports animals, and household pets is a common practice. Frequently, however, the antigen used in a vaccine is not sufficiently immunogenic to raise the antibody titre to levels that are sufficient to provide protection against subsequent challenge or to maintain the potential for mounting these levels over extended time periods. Further, many vaccines are altogether deficient in inducing cell-mediated immunity, which is a primary immune defense against bacterial and viral infection. A considerable amount of research is currently focussed on the development of more potent vaccines and ways to enhance the immunogenicity of antigen-containing preparations. (See e.g., U.S. Pat. Nos. 6,056,961; 6,060,068; 6,063,380; and Li et al., *Science* 288:2219-2222 (2000)).

[0004] Notorious among such "weak" vaccines are hepatitis B vaccines. For example, recombinant vaccines against hepatitis B virus such as Genhevacb (Pasteur Merieux Serums et Vaccines, 58, Avenue Leclerc 69007 Lyon, France), Engerixb (Smith, Kline and Symbol French), and Recombivaxhb (Merck, Sharp, and Dhome) are effective only after at least three injections at 0, 30, and 60 or 180 days, followed by an obligatory booster after one year. (Chedid et al., U.S. Pat. No. 6,063,380). Additionally, many subjects receiving these vaccines respond poorly, if at all. Because many regions of the world are endemic for HBV infection, the poorly immunogenic character of existing HBV vaccines has become an extremely serious problem.

[0005] To obtain a stronger, humoral and/or cellular response, it is common to administer a vaccine in a material that enhances the immune response of the patient to the antigen present in the vaccine. The most commonly used adjuvants for vaccine protocols are oil preparations and alum. (Chedid et al., U.S. Pat. No. 6,063,380). A greater repertoire of safe and effective adjuvants is needed.

[0006] Nucleoside analogs have been widely used in antiviral therapies due to their capacity to reduce viral replication. (Hosoya et al., *J. Inf. Dis.*, 168:641-646 (1993)). Ribavirin (1- β -D-ribofuranosyl-1,2,4-triazole-3-carboxamide) is a synthetic guanosine analog that has been used to

inhibit RNA and DNA virus replication. (Huffinan et al., *Antimicrob. Agents. Chemother.*, 3:235 (1973); Sidwell et al., *Science*, 177:705 (1972)). Ribavirin has been shown to be a competitive inhibitor of inositol mono-phosphate (IMP) dehydrogenase (IMPDH), which converts IMP to IMX (which is then converted to GMP). De Clercq, *Anti viral Agents: characteristic activity spectrum depending on the molecular target with which they interact*, Academic press, Inc., New York N.Y., pp. 1-55 (1993). Intracellular pools of GTP become depleted as a result of long term Ribavirin treatment.

[0007] In addition to antiviral activity, investigators have observed that a few guanosine analogs have an effect on the immune system. (U.S. Pat. Nos. 6,063,772 and 4,950,647). Ribavirin has been shown to inhibit functional humoral immune responses (Peavy et al., *J. Immunol.*, 126:861-864 (1981); Powers et al., *Antimicrob. Agents. Chemother.*, 22:108-114 (1982)) and IgE-mediated modulation of mast cell secretion. (Marquardt et al., *J. Pharmacol. Exp. Therapeutics*, 240:145-149 (1987)). Some investigators report that a daily oral therapy of Ribavirin has an immune modulating effect on humans and mice. (Hultgren et al., *J. Gen. Virol.*, 79:2381-2391 (1998) and Cramp et al., *Gastron. Enterol.*, 118:346-355 (2000)). Nevertheless, the current understanding of the effects of Ribavirin on the immune system is in its infancy.

SUMMARY OF THE INVENTION

[0008] It has been discovered that Ribavirin can be used as an adjuvant to enhance an immune response to an antigen. Embodiments described herein include "strong" vaccine preparations that comprise an antigen and Ribavirin. Generally, these preparations have an amount of Ribavirin that is sufficient to enhance an immune response to the antigen. Other aspects of the invention include methods of enhancing the immune response of an animal, including a human, to an antigen. By one approach, for example, an animal in need of a potent immune response to an antigen is identified and then is provided an amount of Ribavirin together with the antigen that is effective to enhance an immune response in the animal. In some methods, the Ribavirin and the antigen are provided in combination and in others, the Ribavirin and the antigen are provided separately. Thus, several embodiments concern the manufacture and use of vaccine preparations having Ribavirin and an antigen.

[0009] Preferred vaccine compositions comprise Ribavirin and a hepatitis viral antigen. The antigen can be a peptide or nucleic acid-based (e.g., a RNA encoding a peptide antigen or a construct that expresses a peptide antigen when introduced to a subject). HBV antigens that are suitable include, for example, hepatitis B surface antigen (HBsAg), hepatitis core antigen (HBcAg), hepatitis e antigen (HBeAg), and nucleic acids encoding these molecules. Compositions having Ribavirin and an antigen from the hepatitis A virus (HAV) or Ribavirin and a nucleic acid encoding an antigen from HAV are also embodiments. Still further, compositions having Ribavirin and an antigen from the hepatitis C virus (HCV) or Ribavirin and a nucleic acid encoding an antigen from HCV are embodiments.

[0010] Furthermore, compositions having a mixture of the antigens above are embodiments of the present invention.

For example, some compositions comprise a HBV antigen, a HAV antigen, and Ribavirin or a HBV antigen, a HCV antigen, and Ribavirin or a HAV antigen, a HCV antigen, and Ribavirin or a HBV antigen, a HAV antigen, a HCV antigen, and Ribavirin. Other embodiments comprise Ribavirin and a nucleic acid encoding a mixture of the antigens described above. Some embodiments also include other adjuvants, binders, emulsifiers, carriers, and fillers, as known in the art, including, but not limited to, alum, oil, and other compounds that enhance an immune response.

[0011] Preferred methods involve providing an animal in need with a sufficient amount of Ribavirin and a hepatitis viral antigen (e.g., HBV antigen, HAV antigen, HCV antigen, a nucleic acid encoding one of these antigens or any combination thereof). Accordingly, one embodiment includes identifying an animal in need of an enhanced immune response to a hepatitis viral antigen (e.g., an animal at risk or already infected with a hepatitis infection) and providing to said animal an amount of Ribavirin that is effective to enhance an immune response to the hepatitis viral antigen.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] FIG. 1 is a graph showing the humoral response to 10 and 100 μ g recombinant Hepatitis C virus (HCV) non structural 3 protein (NS3), as determined by mean end point titres, when a single dose of 1 mg of Ribavirin was co-administered.

[0013] FIG. 2 is a graph showing the humoral response to 20 μ g recombinant Hepatitis C virus (HCV) non structural 3 protein (NS3), as determined by mean end point titres, when a single dose of 0.1, 1.0, or 10 mg of Ribavirin was co-administered.

[0014] FIG. 3 is a graph showing the effects of a single dose of 1 mg Ribavirin on NS3-specific lymph node proliferative responses, as determined by in vitro recall responses.

DETAILED DESCRIPTION OF THE INVENTION

[0015] It has been discovered that compositions comprising Ribavirin and an antigen can boost an animal's immune response to the antigen. That is, Ribavirin can be used as an "adjuvant," which for the purposes of this disclosure, refers to a compound that has the ability to enhance the immune response to a particular antigen. Such adjuvant activity is manifested by a significant increase in immune-mediated protection against the antigen, and was demonstrated by an increase in the titer of antibody raised to the antigen and an increase in proliferative T cell responses.

[0016] Several vaccine preparations that comprise Ribavirin and an antigen are described herein. Vaccine formulations containing Ribavirin can vary according to the amount of Ribavirin, the form of Ribavirin, and the type of antigen. The antigen can be a peptide or a nucleic acid (e.g., a RNA encoding a peptide antigen or a construct that expresses a peptide antigen when introduced into a subject). Preferred vaccine formulations comprise Ribavirin and a hepatitis viral antigen (e.g., HBV antigen, HAV antigen, HCV antigen, a nucleic acid encoding these molecules, or any combination thereof).

[0017] Methods of enhancing the immune response of an animal, including humans, to an antigen are also described

herein. One method, for example, involves identifying an animal in need of an enhanced immune response to an antigen and providing the animal the antigen and an amount of Ribavirin that is effective to enhance an immune response to the antigen. Preferred methods involve providing the animal in need with Ribavirin and a hepatitis antigen (e.g., HBV antigen, HAV antigen, HCV antigen, a nucleic acid encoding these molecules, or any combination thereof). The section below describes the manufacture of vaccines having Ribavirin and an antigen in greater detail.

[0018] Vaccines Containing Ribavirin

[0019] The vaccines comprise Ribavirin and an antigen and may contain other ingredients including, but not limited to, adjuvants, binding agents, excipients such as stabilizers (to promote long term storage), emulsifiers, thickening agents, salts, preservatives, solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. These vaccine preparations are suitable for treatment of animals either as a preventive measure to avoid a disease or condition or as a therapeutic to treat animals already afflicted with a disease or condition.

[0020] The vaccine compositions can be manufactured in accordance with conventional methods of galenic pharmacy to produce medicinal agents for administration to animals, e.g., mammals including humans. Ribavirin can be obtained from commercial suppliers (e.g., Sigma and ICN). Ribavirin and/or the antigen can be formulated into the vaccine with and without modification. For example, the Ribavirin and/or antigen can be modified or derivatized to make a more stable molecule and/or a more potent adjuvant. By one approach, the stability of Ribavirin and/or an antigen can be enhanced by coupling the molecules to a support such as a hydrophilic polymer (e.g., polyethylene glycol).

[0021] Many more Ribavirin derivatives can be generated using conventional techniques in rational drug design and combinatorial chemistry. For example, Molecular Simulations Inc. (MSI), as well as many other suppliers, provide software that allows one of skill to build a combinatorial library of organic molecules. The C2.Analog Builder program, for example, can be integrated with MSI's suite of Cerius2 molecular diversity software to develop a library of Ribavirin derivatives that can be used with the embodiments described herein. (See e.g., <http://msi.com/life/products/cerius2/index.html>, herein expressly incorporated by reference in its entirety).

[0022] By one approach, the chemical structure of Ribavirin is recorded on a computer readable media and is accessed by one or more modeling software application programs. The C2.Analog Builder program in conjunction with C2Diversity program allows the user to generate a very large virtual library based on the diversity of R-groups for each substituent position, for example. Compounds having the same structure as the modeled Ribavirin derivatives created in the virtual library are then made using conventional chemistry or can be obtained from a commercial source.

[0023] The newly manufactured Ribavirin derivatives are then screened in characterization assays, which determine the extent of adjuvant activity of the molecule and/or the extent of its ability to modulate of an immune response.

Some characterization assays may involve virtual drug screening software, such as C2.Ludi. C2.Ludi is a software program that allows a user to explore databases of molecules (e.g., Ribavirin derivatives) for their ability to interact with the active site of a protein of interest (e.g., RAC2 or another GTP binding protein). Based upon predicted interactions discovered with the virtual drug screening software, the Ribavirin derivatives can be prioritized for further characterization in conventional assays that determine adjuvant activity and/or the extent of a molecule to modulate an immune response.

[0024] Example 1 describes a characterization assay that was used to evaluate the adjuvant activity of Ribavirin.

EXAMPLE 1

[0025] This characterization assay can be used with any Ribavirin derivative or combinations of Ribavirin derivatives to determine the extent of adjuvant activity of the particular vaccine formulation. Accordingly, groups of three to five Balb/c mice (BK Universal, Uppsala, Sweden) were immunized i.p. or s.c. (e.g., at the base of the tail) with 10 μ g or 100 μ g of recombinant hepatitis C virus non-structural 3 (NS3) protein. The rNS3 was dissolved in phosphate buffered saline (PBS) alone or PBS containing 1 mg Ribavirin (obtained from ICN, Costa Mesa, Calif.). Mice were injected with a total volume of 100 μ l per injection.

[0026] At two and four weeks following i.p. immunization, all mice were bled by retro-orbital sampling. Serum samples were collected and analyzed for the presence of antibodies to rNS3. To determine the antibody titer, an enzyme immunoassay (EIA) was performed. (See e.g., Hultgren et al., *J Gen Virol.* 79:2381-91 (1998) and Hultgren et al., *Clin. Diagn. Lab. Immunol.* 4:630-632 (1997), both of which are herein expressly incorporated by reference in their entireties). The antibody levels were recorded as the highest serum dilution giving an optical density at 405 nm more than twice that of non-immunized mice.

[0027] Mice that received 10 μ g or 100 μ g rNS3 mixed with 1 mg Ribavirin in PBS displayed consistently higher levels of NS3 antibodies. The antibody titer that was detected by EIA at two weeks post-immunization is shown in FIG. 1. The vaccine formulations having 1 mg of Ribavirin and either 10 μ g or 100 μ g of rNS3 induced a significantly greater antibody titer than the vaccine formulations composed of only rNS3. This data provides evidence that Ribavirin has an adjuvant effect on the humoral immune response of an animal and thus, enhances the immune response to the antigen.

[0028] The example below describes experiments that were performed to determine the amount of Ribavirin that was needed to elicit an adjuvant effect.

EXAMPLE 2

[0029] To determine the dose of Ribavirin that is required to provide an adjuvant effect, the following experiments were performed. Groups of mice (three per group) were immunized with a 20 μ g rNS3 alone or a mixture of 20 μ g rNS3 and 0.1 mg, 1 mg, or 10 mg Ribavirin. The levels of antibody to the antigen were then determined by EIA. The mean endpoint titers at weeks 1 and 3 were plotted and are shown in FIG. 2. It was discovered that the adjuvant effect

provided by Ribavirin had different kinetics depending on the dose of Ribavirin provided. For example, low doses (<1 mg) of Ribavirin were found to enhance antibody levels at week one but not at week three, whereas, higher doses (1-10 mg) were found to enhance antibody levels at week three. These data further verify that Ribavirin can be administered as an adjuvant and establish that the dose of Ribavirin can modulate the kinetics of the adjuvant effect.

[0030] The example below describes another characterization assay that was performed to evaluate the ability of Ribavirin to modulate a cellular immune response.

EXAMPLE 3

[0031] This characterization assay can be used with any Ribavirin derivative or combinations of Ribavirin derivatives to determine the extent that a particular vaccine formulation modulates a cellular immune response. To determine CD4⁺T cell responses to Ribavirin-containing vaccine, groups of mice were immunized s.c. with either 100 μ g rNS3 in PBS or 100 μ g rNS3 and 1 mg Ribavirin in PBS. The mice were sacrificed ten days post-immunization and their lymph nodes were harvested and drained. In vitro recall assays were then performed. (See e.g., Hultgren et al., *J Gen Virol.* 79:2381-91 (1998) and Hultgren et al., *Clin. Diagn. Lab. Immunol.* 4:630-632 (1997), both of which are herein expressly incorporated by reference in their entireties). The amount of CD4⁺T cell proliferation was determined at 96 h of culture by the incorporation of [³H] thymidine.

[0032] As shown in FIG. 2, mice that were immunized with 100 μ g rNS3 mixed with 1 mg Ribavirin had a much greater T cell proliferative response than mice that were immunized with 100 μ g rNS3 in PBS. This data provides evidence that Ribavirin can enhance a cellular immune response (e.g., by promoting the effective priming of T cells).

[0033] The example below describes the use of Ribavirin in conjunction with a commercial vaccine preparation.

EXAMPLE 4

[0034] The adjuvant effect of Ribavirin was also tested when mixed with two doses of a commercially available vaccine containing HBsAg and alum. (Engerix, SKB). Approximately 0.2 μ g or 2 μ g of Engerix vaccine was mixed with either PBS or 1 mg Ribavirin in PBS and the mixtures were injected intra peritoneally into groups of mice (three per group). A booster containing the same mixture was given on week four and all mice were bled on week six. The serum samples were diluted from 1:60 to 1:37500 and the dilutions were tested by EIA, as described above, except that purified human HBsAg (kindly provided by Professor DL Peterson, Commonwealth University, VA) was used as the solid phase antigen. As shown in TABLE 1, vaccine formulations having Ribavirin enhanced the response to 2 μ g of an existing vaccine despite the fact that the vaccine already contained alum. That is, by adding Ribavirin to a suboptimal vaccine dose (i.e., one that does not induce detectable antibodies alone) antibodies became detectable, providing evidence that the addition of Ribavirin allows for the use of lower antigen amounts in a vaccine formulation without compromising the immune response.

TABLE 1

End point antibody titer to HBsAg in EIA												
0.02 μ g Engerix						0.2 μ g Engerix						
No Ribavirin			1 mg Ribavirin			No Ribavirin			1 mg Ribavirin			
Week	#1	#2	#3	#1	#2	#3	#1	#2	#3	#1	#2	#3
6	<60	<60	<60	<60	<60	<60	<60	<60	<60	300	60	<60

[0035] Any antigen that can be used to generate an immune response in an animal can be combined with Ribavirin so as to prepare the vaccines described herein. That is, antigens that can be incorporated into such a vaccine comprise bacterial antigens, fungal antigens, plant antigens, mold antigens, viral antigens, cancer cell antigens, toxin antigens, chemical antigens, and self-antigens. Although many of these antigens are molecules that induce a significant immune response without an adjuvant, Ribavirin can be administered in conjunction with or combined with "strong" or "weak" antigens to enhance the immune response. In addition, the use of Ribavirin as an adjuvant may allow for the use of lower amounts of vaccine antigens while retaining immunogenicity.

[0036] Preferred embodiments comprise Ribavirin and a viral antigen. Preferred viral antigens are hepatitis viral antigens. Vaccines can comprise, for example, Ribavirin and an HBV antigen, HAV antigen, HCV antigen or any combination of these antigens. Preferred viral antigens include hepatitis B surface antigen (HBsAg), hepatitis core antigen (HBcAg), and hepatitis E antigen (HBeAg).

[0037] For example, HCV vaccine embodiments comprise Ribavirin and a HCV peptide of at least 3 consecutive amino acids of SEQ. ID. No. 1. That is, a vaccine embodiment can have Ribavirin and a HCV peptide with a length of at least 3-10 consecutive amino acids, 10-50 consecutive amino acids, 50-100 consecutive amino acids, 100-200 consecutive amino acids, 200-400 consecutive amino acids, 400-800 consecutive amino acids, 800-1200 consecutive amino acids, 1200-1600 consecutive amino acids, 1600-2000 consecutive amino acids, 2000-2500 consecutive amino acids, and 2500-3011 consecutive amino acids of SEQ. ID. No. 1. Preferred HCV vaccines comprise Ribavirin and a peptide of at least 3 consecutive amino acids of HCV core protein (SEQ. ID. No. 2), HCV E1 protein (SEQ. ID. No. 3), HCV E2 protein (SEQ. ID. No. 4), HCV NS2 (SEQ. ID. No. 5), HCV NS3 (SEQ. ID. No. 6), HCV NS4A (SEQ. ID. No. 7), HCV NS4B (SEQ. ID. No. 8), or HCV NS5A/B (SEQ. ID. No. 9). That is, preferred HCV vaccines can comprise Ribavirin and a peptide with a length of at least 3-10 consecutive amino acids, 10-50 consecutive amino acids, 50-100 consecutive amino acids, 100-200 consecutive amino acids, 200-400 consecutive amino acids, 400-800 consecutive amino acids, and 800-1040 consecutive amino acids of any one of (SEQ. ID. Nos. 2-9).

[0038] Similarly, preferred HBV vaccine embodiments comprise Ribavirin and a HBV peptide of at least 3 consecutive amino acids of HBsAg (SEQ. ID. No. 10) or HBcAg and HBeAg (SEQ. ID. No. 11). That is, a vaccine embodiment can have Ribavirin and a HBV peptide with a length of at least 3-10 consecutive amino acids, 10-50

consecutive amino acids, 50-100 consecutive amino acids, 100-150 consecutive amino acids, 150-200 consecutive amino acids, and 200-226 consecutive amino acids of either SEQ. ID. No. 10 or SEQ. ID. No. 11. Further, preferred HAV embodiments comprise Ribavirin and a HAV peptide with a length of at least 3-10 consecutive amino acids, 10-50 consecutive amino acids, 50-100 consecutive amino acids, 100-200 consecutive amino acids, 200-400 consecutive amino acids, 400-800 consecutive amino acids, 800-1200 consecutive amino acids, 1200-1600 consecutive amino acids, 1600-2000 consecutive amino acids, and 2000-2227 consecutive amino acids of SEQ. ID. No. 12.

[0039] In addition to peptide antigens, nucleic acid-based antigens can be used in the vaccine compositions described herein. Various nucleic acid-based vaccines are known and it is contemplated that these compositions and approaches to immunotherapy can be augmented by introducing Ribavirin (See e.g., U.S. Pat. No. 5589466, herein expressly incorporated by reference in its entirety).

[0040] By one approach, for example, a gene encoding a polypeptide antigen of interest is cloned into an expression vector capable of expressing the polypeptide when introduced into a subject. The expression construct is introduced into the subject in a mixture of Ribavirin or in conjunction with Ribavirin (e.g., Ribavirin is administered shortly after the expression construct at the same site). Alternatively, RNA encoding a polypeptide antigen of interest is provided to the subject in a mixture with Ribavirin or in conjunction with Ribavirin. Where the polynucleotide is to be DNA, promoters suitable for use in various vertebrate systems are well known. For example, for use in murine systems, suitable strong promoters include RSV LTR, MPSV LTR, SV40 IEP, and metallothionein promoter. In humans, on the other hand, promoters such as CMV IEP can be used. All forms of DNA, whether replicating or non-replicating, which do not become integrated into the genome, and which are expressible, can be used.

[0041] Preferred nucleic acid-based antigens include a nucleotide sequence of at least 9 consecutive nucleotides of HCV (SEQ. ID. No. 13), HBV (SEQ. ID. No. 14), or HAV (SEQ. ID. No. 15). That is, a nucleic acid based antigen can comprise at least 9-25 consecutive nucleotides, 25-50 consecutive nucleotides, 50-100 consecutive nucleotides, 100-200 consecutive nucleotides, 200-500 consecutive nucleotides, 500-1000 consecutive nucleotides, 1000-2000 consecutive nucleotides, 2000-4000 consecutive nucleotides, 4000-8000 consecutive nucleotides, and 8000-9416 consecutive nucleotides of any one of SEQ. ID. Nos. 13-15 or an RNA that corresponds to these sequences.

[0042] The example below describes one approach for using a nucleic acid-based antigen in conjunction with Ribavirin.

EXAMPLE 5

[0043] The following describes an approach to immunize an animal with a vaccine comprising a nucleic acid-based antigen and Ribavirin. Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. One group of mice are injected with approximately 20 μ g of an expression construct having the gp-120 gene, driven by a cytomegalovirus (CMV) promoter and second group of mice are injected with approximately 5 μ g of capped in vitro transcribed RNA (e.g., SP6, T7, or T3 (Ambion)) encoding gp-120. These two groups are controls. A third group of mice is injected with approximately 20 μ g of the expression vector having the gp-120 gene and the CMV promoter mixed with 1 mg of Ribavirin and a fourth group of mice is injected with approximately 5 μ g of capped in vitro transcribed RNA mixed with 1 mg Ribavirin. The vaccines are injected in 0.1 ml of solution (PBS) in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is then closed with stainless steel clips.

[0044] Blood samples are obtained prior to the injection (Day 0) and up to more than 40 days post injection. The serum from each sample is serially diluted and assayed in a standard ELISA technique assay for the detection of antibody, using recombinant gp-120 protein made in yeast as the antigen. Both IgG and IgM antibodies specific for gp-120 will be detected in all samples, however, groups three and four, which contained the Ribavirin, will exhibit a greater immune response to the gp-120 as measured by the amount and/or titer of antibody detected in the sera.

[0045] Many other ingredients can be present in the vaccine. For example, the Ribavirin and antigen can be employed in admixture with conventional excipients (e.g., pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral, enteral (e.g., oral) or topical application that do not deleteriously react with the Ribavirin and/or antigen). Suitable pharmaceutically acceptable carriers include, but are not limited to, water, salt solutions, alcohols, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelatine, carbohydrates such as lactose, amylose or starch, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxy methylcellulose, polyvinyl pyrrolidone, etc. Many more suitable carriers are described in *Remington's Pharmaceutical Sciences*, 15th Edition, Easton: Mack Publishing Company, pages 1405-1412 and 1461-1487 (1975) and *The National Formulary XIV*, 14th Edition, Washington, American Pharmaceutical Association (1975), herein expressly incorporated by reference in their entireties. Vaccines can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, flavoring and/or aromatic substances and the like that do not deleteriously react with Ribavirin or the antigen.

[0046] The effective dose and method of administration of a particular vaccine formulation can vary based on the individual patient and the type and stage of the disease, as well as other factors known to those of skill in the art. Therapeutic efficacy and toxicity of the vaccines can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., ED50 (the dose therapeutically effective in 50% of the population). The data obtained from cell culture assays and animal studies can be used to formulate a range of dosage for human use. The dosage of the vaccines lies preferably within a range of circulating concentrations that include the ED50 with no toxicity. The dosage varies within this range depending upon the type of Ribavirin derivative and antigen, the dosage form employed, the sensitivity of the patient, and the route of administration.

[0047] Since Ribavirin has been on the market for several years, many dosage forms and routes of administration are known. All known dosage forms and routes of administration can be provided within the context of the embodiments described herein. Preferably, an amount of Ribavirin that is effective to enhance an immune response to an antigen in an animal can be considered to be an amount that is sufficient to achieve a blood serum level of antigen approximately 0.25-12.5 μ g/ml in the animal, preferably, about 2.5 μ g/ml. In some embodiments, the amount of Ribavirin is determined according to the body weight of the animal to be given the vaccine. Accordingly, the amount of Ribavirin in a vaccine formulation can be from about 0.1-6.0 mg/kg body weight. That is, some embodiments have an amount of Ribavirin that corresponds to approximately 0.1-1.0 mg/kg, 1.1-2.0 mg/kg, 2.1-3.0 mg/kg, 3.1-4.0 mg/kg, 4.1-5.0 mg/kg, 5.1, and 6.0 mg/kg body weight of an animal. More conventionally, the vaccines contain approximately 0.25 mg-2000 mg of Ribavirin. That is, some embodiments have approximately 250 μ g, 500 μ g, 1 mg, 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 1 g, 1.1 g, 1.2 g, 1.3 g, 1.4 g, 1.5 g, 1.6 g, 1.7 g, 1.8 g, 1.9 g, and 2 g of Ribavirin.

[0048] Vaccines comprising various antigens and amounts of these antigens have been provided to animals for many years. Thus, conventional vaccine preparations can be modified by adding an amount of Ribavirin that is sufficient to enhance an immune response to the antigen. That is, existing conventional vaccine formulations can be modified by simply adding Ribavirin to the preparation or by administering the conventional vaccine in conjunction with Ribavirin (e.g., shortly before or after providing the antigen). As one of skill in the art will appreciate, the amount of antigens in a vaccine can vary depending on the type of antigen and its immunogenicity. The amount of antigens in the vaccines can vary accordingly. Nevertheless, as a general guide, the vaccines can have approximately 0.25 mg-2000 mg of an antigen (e.g., a hepatitis viral antigen).

[0049] In some approaches described herein, the exact amount of Ribavirin and/or antigen is chosen by the individual physician in view of the patient to be treated. Further, the amounts of Ribavirin can be added in combination to or separately from the same or equivalent amount of antigen and these amounts can be adjusted during a particular vaccination protocol so as to provide sufficient levels in light of patient-specific or antigen-specific considerations. In this

vein, patient-specific and antigen-specific factors that can be taken into account include, but are not limited to, the severity of the disease state of the patient, age, and weight of the patient, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy.

[0050] Routes of administration of the vaccines described herein include, but are not limited to, transdermal, parenteral, gastrointestinal, transbronchial, and transalveolar. Transdermal administration can be accomplished by application of a cream, rinse, gel, etc. capable of allowing Ribavirin and antigen to penetrate the skin. Parenteral routes of administration include, but are not limited to, electrical or direct injection such as direct injection into a central venous line, intravenous, intramuscular, intraperitoneal, intradermal, or subcutaneous injection. Gastrointestinal routes of administration include, but are not limited to, ingestion and rectal. Transbronchial and transalveolar routes of administration include, but are not limited to, inhalation, either via the mouth or intranasally.

[0051] Compositions having Ribavirin and an antigen that are suitable for transdermal administration include, but are not limited to, pharmaceutically acceptable suspensions, oils, creams, and ointments applied directly to the skin or incorporated into a protective carrier such as a transdermal device ("transdermal patch"). Examples of suitable creams, ointments, etc. can be found, for instance, in the Physician's Desk Reference. Examples of suitable transdermal devices are described, for instance, in U.S. Pat. No. 4,818,540 issued Apr. 4, 1989 to Chinen, et al., herein expressly incorporated by reference in its entirety.

[0052] Compositions having Ribavirin and an antigen that are suitable for parenteral administration include, but are not limited to, pharmaceutically acceptable sterile isotonic solutions. Such solutions include, but are not limited to, saline, phosphate buffered saline and oil preparations for injection into a central venous line, intravenous, intramuscular, intraperitoneal, intradermal, or subcutaneous injection.

[0053] Compositions having Ribavirin and an antigen that are suitable for transbronchial and transalveolar administration include, but not limited to, various types of aerosols for inhalation. Devices suitable for transbronchial and transalveolar administration of these are also embodiments. Such devices include, but are not limited to, atomizers and vaporizers. Many forms of currently available atomizers and vaporizers can be readily adapted to deliver vaccines having Ribavirin and an antigen.

[0054] Compositions having Ribavirin and an antigen that are suitable for gastrointestinal administration include, but not limited to, pharmaceutically acceptable powders, pills or liquids for ingestion and suppositories for rectal administration.

[0055] Once the vaccine comprising Ribavirin and an antigen has been obtained, it can be administered to a subject in need to treat or prevent diseases. The next section describes methods that employ the vaccines described above.

[0056] Methods of use of Vaccines that Contain Ribavirin

[0057] The vaccines containing Ribavirin and an antigen can be used to treat and prevent a vast spectrum of diseases

and can enhance the immune response of an animal to an antigen. As one of skill in the art will appreciate conventional vaccines have been administered to subjects in need of treatment or prevention of bacterial diseases, viral diseases, fungal diseases, and cancer. Because the vaccines described herein include conventional vaccines, which have been modified by the addition of Ribavirin, the methods described herein include the treatment and prevention of a disease using a vaccine that comprises an antigen and Ribavirin.

[0058] Preferred embodiments concern methods of treating or preventing hepatitis infection. In these embodiments, an animal in need is provided a hepatitis antigen (e.g., a peptide antigen or nucleic acid-based antigen) and an amount of Ribavirin sufficient to exhibit an adjuvant activity in said animal. Accordingly, an animal can be identified as one in need by using currently available diagnostic testing or clinical evaluation. The range of hepatitis viral antigens that can be used with these embodiments is diverse. Preferred hepatitis viral antigens include an HBV antigen, an HAV antigen, an HCV antigen, nucleic acids encoding these antigens, or any combination thereof. Highly preferred embodiments include an HBV antigen selected from the group consisting of hepatitis B surface antigen (HBsAg), hepatitis core antigen (HBcAg), and hepatitis E antigen (HBeAg), in particular, the peptide and nucleic acid-based antigens described supra. The Ribavirin and antigen can be provided separately or in combination, and other adjuvants (e.g., oil, alum, or other agents that enhance an immune response) can also be provided to the animal in need. Thus, preferred embodiments include methods of treating or preventing hepatitis in an animal (e.g., HBV) by identifying an infected animal or an animal at risk of infection and providing said animal a hepatitis antigen (e.g., HBsAg, HBcAg, and HBeAg) and an amount of Ribavirin sufficient to exhibit adjuvant activity.

[0059] Other embodiments include methods of enhancing an immune response to an antigen by providing an animal in need with an amount of Ribavirin that is effective to enhance said immune response. In these embodiments, an animal in need of an enhanced immune response to an antigen is identified by using currently available diagnostic testing or clinical evaluation. Oftentimes these individuals will be suffering from a disease (e.g., bacterial, fungal, mold, viral, or cancer) or are at risk from contracting the disease. However, an animal in need of an enhanced immune response can be an animal that has been poisoned (e.g., bit by a poisonous insect or animal) or that has been exposed to a toxin or other toxic compound. Once identified, these animals are provided an appropriate antigen and an amount of Ribavirin effective to enhance an immune response in the animal.

[0060] As above, the hepatitis viral antigens that can be used with these embodiments include, but are not limited to, an HBV antigen, an HAV antigen, an HCV antigen, a nucleic acid encoding these molecules, or any combination thereof. Highly preferred embodiments include an HBV antigen selected from the group consisting of hepatitis B surface antigen (HBsAg), hepatitis core antigen (HBcAg), and hepatitis E antigen (HBeAg), in particular, the peptide and nucleic acid-based antigens described supra. The Ribavirin and antigen can be provided separately or in combination, and other adjuvants (e.g., oil, alum, or other agents that enhance an immune response) can also be provided to the

animal in need. Thus, preferred embodiments include methods of enhancing an immune response to a hepatitis antigen (e.g., HBV) by identifying an animal in need and providing the animal a hepatitis antigen (e.g., HBsAg, HBcAg, and HBeAg) and an amount of Ribavirin that is effective to enhance an immune response in the animal.

[0061] Although the invention has been described with reference to embodiments and examples, it should be understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the following claims. All references cited herein are hereby expressly incorporated by reference.

SEQUENCE LISTING

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Gly Val Tyr Leu Leu Pro Arg Arg Gly Pro Arg Leu Gly Val Arg Ala
35 40 45

Thr Arg Lys Thr Ser Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro
50 55 60

Ile Pro Lys Ala Arg Arg Pro Glu Gly Arg Thr Trp Ala Gln Pro Gly
65 70 75 80

Tyr Pro Trp Pro Leu Tyr Gly Asn Glu Gly Cys Gly Trp Ala Gly Trp
85 90 95

Leu Leu Ser Pro Arg Gly Ser Arg Pro Ser Trp Gly Pro Thr Asp Pro
100 105 110

Arg Arg Arg Ser Arg Asn Leu Gly Lys Val Ile Asp Thr Leu Thr Cys
115 120 125

Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala Pro Leu
130 135 140

Gly Gly Ala Ala Arg Ala Leu Ala His Gly Val Arg Val Leu Glu Asp
145 150 155 160

Gly Val Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe Ser Ile
165 170 175

Phe Leu Leu Ala Leu Leu
180

<210> SEQ ID NO 3
<211> LENGTH: 197
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Hepatitis C virus E1 protein sequence

<400> SEQUENCE: 3

Ser Cys Leu Thr Val Pro Ala Ser Ala Tyr Gln Val Arg Asn Ser Ser
1 5 10 15

Gly Leu Tyr His Val Thr Asn Asp Cys Pro Asn Ser Ser Val Val Tyr
20 25 30

Glu Ala Ala Asp Ala Ile Leu His Thr Pro Gly Cys Val Pro Cys Val
35 40 45

Arg Glu Gly Asn Ala Ser Arg Cys Trp Val Ala Val Thr Pro Thr Val
50 55 60

Ala Thr Arg Asp Gly Lys Leu Pro Thr Thr Gln Leu Arg Arg His Ile
65 70 75 80

Asp Leu Leu Val Gly Ser Ala Thr Leu Cys Ser Ala Leu Tyr Val Gly
85 90 95

Asp Leu Cys Gly Ser Val Phe Leu Val Gly Gln Leu Phe Thr Phe Ser
100 105 110

Pro Arg His His Trp Thr Thr Gln Asp Cys Asn Cys Ser Ile Tyr Pro
115 120 125

Gly His Ile Thr Gly His Arg Met Ala Trp Asn Met Met Met Asn Trp
130 135 140

Ser Pro Thr Ala Ala Leu Val Val Ala Gln Leu Leu Arg Ile Pro Gln
145 150 155 160

Ala Ile Met Asp Met Ile Ala Gly Ala His Trp Gly Val Leu Ala Gly
165 170 175

Ile Lys Tyr Phe Ser Met Val Gly Asn Trp Ala Lys Val Leu Val Val
180 185 190

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Leu Leu Leu Phe Ala
195

<210> SEQ ID NO 4
<211> LENGTH: 350
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Hepatitis C virus E2 protein sequence

<400> SEQUENCE: 4

Gly Val Asp Ala Glu Thr His Val Thr Gly Gly Asn Ala Gly Arg Thr
1 5 10 15
Thr Ala Gly Leu Val Gly Leu Leu Thr Pro Gly Ala Lys Gln Asn Ile
20 25 30
Gln Leu Ile Asn Thr Asn Gly Ser Trp His Ile Asn Ser Thr Ala Leu
35 40 45
Asn Cys Asn Glu Ser Leu Asn Thr Gly Trp Leu Ala Gly Leu Phe Tyr
50 55 60
Gln His Lys Phe Asn Ser Ser Gly Cys Pro Glu Arg Leu Ala Ser Cys
65 70 75 80
Arg Arg Leu Thr Asp Phe Ala Gln Gly Trp Gly Pro Ile Ser Tyr Ala
85 90 95
Asn Gly Ser Gly Leu Asp Glu Arg Pro Tyr Cys Trp His Tyr Pro Pro
100 105 110
Arg Pro Cys Gly Ile Val Pro Ala Lys Ser Val Cys Gly Pro Val Tyr
115 120 125
Cys Phe Thr Pro Ser Pro Val Val Val Gly Thr Thr Asp Arg Ser Gly
130 135 140
Ala Pro Thr Tyr Ser Trp Gly Ala Asn Asp Thr Asp Val Phe Val Leu
145 150 155 160
Asn Asn Thr Arg Pro Pro Leu Gly Asn Trp Phe Gly Cys Thr Trp Met
165 170 175
Asn Ser Thr Gly Phe Thr Lys Val Cys Gly Ala Pro Pro Cys Val Ile
180 185 190
Gly Gly Val Gly Asn Asn Thr Leu Leu Cys Pro Thr Asp Cys Phe Arg
195 200 205
Lys Tyr Pro Glu Ala Thr Tyr Ser Arg Cys Gly Ser Gly Pro Arg Ile
210 215 220
Thr Pro Arg Cys Met Val Asp Tyr Pro Tyr Arg Leu Trp His Tyr Pro
225 230 235 240
Cys Thr Ile Asn Tyr Thr Ile Phe Lys Val Arg Met Tyr Val Gly Gly
245 250 255
Val Glu His Arg Leu Glu Ala Ala Cys Asn Trp Thr Arg Gly Glu Arg
260 265 270
Cys Asp Leu Glu Asp Arg Asp Arg Ser Glu Leu Ser Pro Leu Leu Leu
275 280 285
Ser Thr Thr Gln Trp Gln Val Leu Pro Cys Ser Phe Thr Thr Leu Pro
290 295 300
Ala Leu Ser Thr Gly Leu Ile His Leu His Gln Asn Ile Val Asp Val
305 310 315 320
Gln Tyr Leu Tyr Gly Val Gly Ser Ser Ile Ala Ser Trp Ala Ile Lys
325 330 335

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Trp Glu Tyr Val Val Leu Leu Phe Leu Leu Leu Ala Asp Ala
 340 345 350

<210> SEQ ID NO 5
 <211> LENGTH: 315
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Hepatitis C virus NS2 protein sequence

<400> SEQUENCE: 5

Arg Val Cys Ser Cys Leu Trp Met Met Leu Leu Ile Ser Gln Ala Glu
 1 5 10 15
 Ala Ala Leu Glu Asn Leu Val Ile Leu Asn Ala Ala Ser Leu Ala Gly
 20 25 30
 Thr His Gly Leu Val Ser Phe Leu Val Phe Phe Cys Phe Ala Trp Tyr
 35 40 45
 Leu Lys Gly Arg Trp Val Pro Gly Ala Val Tyr Ala Leu Tyr Gly Met
 50 55 60
 Trp Pro Leu Leu Leu Leu Leu Leu Ala Leu Pro Gln Arg Ala Tyr Ala
 65 70 75 80
 Leu Asp Thr Glu Val Ala Ala Ser Cys Gly Gly Val Val Leu Val Gly
 85 90 95
 Leu Met Ala Leu Thr Leu Ser Pro Tyr Tyr Lys Arg Tyr Ile Ser Trp
 100 105 110
 Cys Met Trp Trp Leu Gln Tyr Phe Leu Thr Arg Val Glu Ala Gln Leu
 115 120 125
 His Val Trp Val Pro Pro Leu Asn Val Arg Gly Gly Arg Asp Ala Val
 130 135 140
 Ile Leu Leu Thr Cys Val Val His Pro Ala Leu Val Phe Asp Ile Thr
 145 150 155 160
 Lys Leu Leu Leu Ala Ile Phe Gly Pro Leu Trp Ile Leu Gln Ala Ser
 165 170 175
 Leu Leu Lys Val Pro Tyr Phe Val Arg Val Gln Gly Leu Leu Arg Ile
 180 185 190
 Cys Ala Leu Ala Arg Lys Ile Ala Gly Gly His Tyr Val Gln Met Ala
 195 200 205
 Ile Ile Lys Leu Gly Ala Leu Thr Gly Thr Cys Val Tyr Asn His Leu
 210 215 220
 Ala Pro Leu Arg Asp Trp Ala His Asn Gly Leu Arg Asp Leu Ala Val
 225 230 235 240
 Ala Val Glu Pro Val Val Phe Ser Arg Met Glu Thr Lys Leu Ile Thr
 245 250 255
 Trp Gly Ala Asp Thr Ala Ala Cys Gly Asp Ile Ile Asn Gly Leu Pro
 260 265 270
 Val Ser Ala Arg Arg Gly Gln Glu Ile Leu Leu Gly Pro Ala Asp Gly
 275 280 285
 Met Val Ser Lys Gly Trp Arg Leu Leu Ala Pro Ile Thr Ala Tyr Ala
 290 295 300
 Gln Gln Thr Arg Gly Leu Leu Gly Cys Ile Ile
 305 310 315

<210> SEQ ID NO 6

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<211> LENGTH: 613
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Hepatitis C virus NS3 protein sequence

<400> SEQUENCE: 6

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Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val Glu Gly Glu Val Gln
 1           5           10           15

Ile Val Ser Thr Ala Thr Gln Thr Phe Leu Ala Thr Cys Ile Asn Gly
      20           25           30

Val Cys Trp Thr Val Tyr His Gly Ala Gly Thr Arg Thr Ile Ala Ser
      35           40           45

Pro Lys Gly Pro Val Ile Gln Thr Tyr Thr Asn Val Asp Gln Asp Leu
      50           55           60

Val Gly Trp Pro Ala Pro Gln Gly Ser Arg Ser Leu Thr Pro Cys Thr
      65           70           75           80

Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg His Ala Asp Val Ile
      85           90           95

Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser Leu Leu Ser Pro Arg
      100          105          110

Pro Ile Ser Tyr Leu Lys Gly Ser Ser Gly Gly Pro Leu Leu Cys Pro
      115          120          125

Thr Gly His Ala Val Gly Leu Phe Arg Ala Ala Val Cys Thr Arg Gly
      130          135          140

Val Ala Lys Ala Val Asp Phe Ile Pro Val Glu Asn Leu Glu Thr Thr
      145          150          155          160

Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser Pro Pro Ala Val Pro
      165          170          175

Gln Ser Phe Gln Val Ala His Leu His Ala Pro Thr Gly Ser Gly Lys
      180          185          190

Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Lys Gly Tyr Lys Val Leu
      195          200          205

Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr Met
      210          215          220

Ser Lys Ala His Gly Val Asp Pro Asn Ile Arg Thr Gly Val Arg Thr
      225          230          235          240

Ile Thr Thr Gly Ser Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu
      245          250          255

Ala Asp Ala Gly Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp
      260          265          270

Glu Cys His Ser Thr Asp Ala Thr Ser Ile Ser Gly Ile Gly Thr Val
      275          280          285

Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr
      290          295          300

Ala Thr Pro Pro Gly Ser Val Thr Val Ser His Pro Asn Ile Glu Glu
      305          310          315          320

Val Ala Leu Ser Thr Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile
      325          330          335

Pro Leu Glu Val Ile Lys Gly Gly Arg His Leu Ile Phe Cys His Ser
      340          345          350

Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu Val Ala Leu Gly Ile
      355          360          365

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Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro Thr
 370                               375                               380

Ser Gly Asp Val Val Val Val Ser Thr Asp Ala Leu Met Thr Gly Phe
 385                               390                               395                               400

Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr Gln
                               405                               410                               415

Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Thr Thr
                               420                               425                               430

Leu Pro Gln Asp Ala Val Ser Arg Thr Gln Arg Arg Gly Arg Thr Gly
                               435                               440                               445

Arg Gly Lys Pro Gly Ile Tyr Arg Phe Val Ala Pro Gly Glu Arg Pro
                               450                               455                               460

Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly
 465                               470                               475                               480

Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr Thr Val Arg Leu Arg
                               485                               490                               495

Ala Tyr Met Asn Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu Gly
                               500                               505                               510

Phe Trp Glu Gly Val Phe Thr Gly Leu Thr His Ile Asp Ala His Phe
                               515                               520                               525

Leu Ser Gln Thr Lys Gln Ser Gly Glu Asn Phe Pro Tyr Leu Val Ala
 530                               535                               540

Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser Trp
 545                               550                               555                               560

Asp Gln Met Arg Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His Gly
                               565                               570                               575

Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Val Thr
                               580                               585                               590

Leu Thr His Pro Ile Thr Lys Tyr Ile Met Thr Cys Met Ser Ala Asp
 595                               600                               605

Leu Glu Val Val Thr
 610

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<210> SEQ ID NO 7
<211> LENGTH: 54
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Hepatitis C virus NS4A protein sequence

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<400> SEQUENCE: 7

```

Ser Thr Trp Val Leu Val Gly Gly Val Leu Ala Ala Leu Ala Ala Tyr
 1                               5                               10                               15

Cys Leu Ser Thr Gly Cys Val Val Ile Val Gly Arg Ile Val Leu Ser
                               20                               25                               30

Gly Lys Pro Ala Ile Ile Pro Asp Arg Glu Val Leu Tyr Gln Glu Phe
 35                               40                               45

Asp Glu Met Glu Glu Cys
 50

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<210> SEQ ID NO 8
<211> LENGTH: 260
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:

<223> OTHER INFORMATION: Hepatitis C virus NS4B protein sequence

<400> SEQUENCE: 8

```

Ser Gln His Leu Pro Tyr Ile Glu Gln Gly Met Met Leu Ala Glu Gln
 1             5             10             15

Phe Lys Gln Lys Ala Leu Gly Leu Leu Gln Thr Ala Ser Arg His Ala
      20             25             30

Glu Val Ile Thr Pro Ala Val Gln Thr Asn Trp Gln Lys Leu Glu Val
      35             40             45

Phe Trp Ala Lys His Met Trp Asn Phe Ile Ser Gly Ile Gln Tyr Leu
      50             55             60

Ala Gly Leu Ser Thr Leu Pro Gly Asn Pro Ala Ile Ala Ser Leu Met
      65             70             75             80

Ala Phe Thr Ala Ala Val Thr Ser Pro Leu Thr Thr Gly Gln Thr Leu
      85             90             95

Leu Phe Asn Ile Leu Gly Gly Trp Val Ala Ala Gln Leu Ala Ala Pro
      100            105            110

Gly Ala Ala Thr Ala Phe Val Gly Ala Gly Leu Ala Gly Ala Ala Leu
      115            120            125

Asp Ser Val Gly Leu Gly Lys Val Leu Val Asp Ile Leu Ala Gly Tyr
      130            135            140

Gly Ala Gly Val Ala Gly Ala Leu Val Ala Phe Lys Ile Met Ser Gly
      145            150            155            160

Glu Val Pro Ser Thr Glu Asp Leu Val Asn Leu Leu Pro Ala Ile Leu
      165            170            175

Ser Pro Gly Ala Leu Ala Val Gly Val Val Phe Ala Ser Ile Leu Arg
      180            185            190

Arg Arg Val Gly Pro Gly Glu Gly Ala Val Gln Trp Met Asn Arg Leu
      195            200            205

Ile Ala Phe Ala Ser Arg Gly Asn His Val Ser Pro Thr His Tyr Val
      210            215            220

Pro Glu Ser Asp Ala Ala Ala Arg Val Thr Ala Ile Leu Ser Ser Leu
      225            230            235            240

Thr Val Thr Gln Leu Leu Arg Arg Leu His Gln Trp Ile Ser Ser Glu
      245            250            255

Cys Thr Thr Pro
      260

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<210> SEQ ID NO 9

<211> LENGTH: 1040

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Hepatitis C virus NS5A/B protein sequence

<400> SEQUENCE: 9

```

Cys Ser Gly Ser Trp Leu Arg Asp Ile Trp Asp Trp Ile Cys Glu Val
 1             5             10             15

Leu Ser Asp Phe Lys Thr Trp Leu Lys Ala Lys Leu Met Pro Gln Leu
      20             25             30

Pro Gly Ile Pro Phe Val Ser Cys Gln Arg Gly Tyr Arg Gly Val Trp
      35             40             45

Arg Gly Asp Gly Ile Met His Thr Arg Cys His Cys Gly Ala Glu Ile

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50	55	60
Thr Gly His Val Lys Asn Gly Thr Met Arg Ile Val Gly Pro Arg Thr 65 70 75 80		
Cys Lys Asn Met Trp Ser Gly Thr Phe Phe Ile Asn Ala Tyr Thr Thr 85 90 95		
Gly Pro Cys Thr Pro Leu Pro Ala Pro Asn Tyr Lys Phe Ala Leu Trp 100 105 110		
Arg Val Ser Ala Glu Glu Tyr Val Glu Ile Arg Arg Val Gly Asp Phe 115 120 125		
His Tyr Val Ser Gly Met Thr Thr Asp Asn Leu Lys Cys Pro Cys Gln 130 135 140		
Ile Pro Ser Pro Glu Phe Phe Thr Glu Leu Asp Gly Val Arg Leu His 145 150 155 160		
Arg Phe Ala Pro Pro Cys Lys Pro Leu Leu Arg Glu Glu Val Ser Phe 165 170 175		
Arg Val Gly Leu His Glu Tyr Pro Val Gly Ser Gln Leu Pro Cys Glu 180 185 190		
Pro Glu Pro Asp Val Ala Val Leu Thr Ser Met Leu Thr Asp Pro Ser 195 200 205		
His Ile Thr Ala Glu Ala Ala Gly Arg Arg Leu Ala Arg Gly Ser Pro 210 215 220		
Pro Ser Met Ala Ser Ser Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu 225 230 235 240		
Lys Ala Thr Cys Thr Ala Asn His Asp Ser Pro Asp Ala Glu Leu Ile 245 250 255		
Glu Ala Asn Leu Leu Trp Arg Gln Glu Met Gly Gly Asn Ile Thr Arg 260 265 270		
Val Glu Ser Glu Asn Lys Val Val Ile Leu Asp Ser Phe Asp Pro Leu 275 280 285		
Val Ala Glu Glu Asp Glu Arg Glu Val Ser Val Pro Ala Glu Ile Leu 290 295 300		
Arg Lys Ser Arg Arg Phe Ala Pro Ala Leu Pro Val Trp Ala Arg Pro 305 310 315 320		
Asp Tyr Asn Pro Leu Leu Val Glu Thr Trp Lys Lys Pro Asp Tyr Glu 325 330 335		
Pro Pro Val Val His Gly Cys Pro Leu Pro Pro Pro Arg Ser Pro Pro 340 345 350		
Val Pro Pro Pro Arg Lys Lys Arg Thr Val Val Leu Thr Glu Ser Thr 355 360 365		
Leu Pro Thr Ala Leu Ala Glu Leu Ala Thr Lys Ser Phe Gly Ser Ser 370 375 380		
Ser Thr Ser Gly Ile Thr Gly Asp Asn Thr Thr Thr Ser Ser Glu Pro 385 390 395 400		
Ala Pro Ser Gly Cys Pro Pro Asp Ser Asp Val Glu Ser Tyr Ser Ser 405 410 415		
Met Pro Pro Leu Glu Gly Glu Pro Gly Asp Pro Asp Leu Ser Asp Gly 420 425 430		
Ser Trp Ser Thr Val Ser Ser Gly Ala Asp Thr Glu Asp Val Val Cys 435 440 445		
Cys Ser Met Ser Tyr Ser Trp Thr Gly Ala Leu Val Thr Pro Cys Ala 450 455 460		

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Ala Glu Glu Gln Lys Leu Pro Ile Asn Ala Leu Ser Asn Ser Leu Leu
 465 470 475 480

Arg His His Asn Leu Val Tyr Ser Thr Thr Ser Arg Ser Ala Cys Gln
 485 490 495

Arg Lys Lys Lys Val Thr Phe Asp Arg Leu Gln Val Leu Asp Ser His
 500 505 510

Tyr Gln Asp Val Leu Lys Glu Val Lys Ala Ala Ala Ser Lys Val Lys
 515 520 525

Ala Asn Leu Leu Ser Val Glu Glu Ala Cys Ser Leu Ala Pro Pro His
 530 535 540

Ser Ala Lys Ser Lys Phe Gly Tyr Gly Ala Lys Asp Val Arg Cys His
 545 550 555 560

Ala Arg Lys Ala Val Ala His Ile Asn Ser Val Trp Lys Asp Leu Leu
 565 570 575

Glu Asp Ser Val Thr Pro Ile Asp Thr Thr Ile Met Ala Lys Asn Glu
 580 585 590

Val Phe Cys Val Gln Pro Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu
 595 600 605

Ile Val Phe Pro Asp Leu Gly Val Arg Val Cys Glu Lys Met Ala Leu
 610 615 620

Tyr Asp Val Val Ser Lys Leu Pro Leu Ala Val Met Gly Ser Ser Tyr
 625 630 635 640

Gly Phe Gln Tyr Ser Pro Gly Gln Arg Val Glu Phe Leu Val Gln Ala
 645 650 655

Trp Lys Ser Lys Lys Thr Pro Met Gly Leu Ser Tyr Asp Thr Arg Cys
 660 665 670

Phe Asp Ser Thr Val Thr Glu Ser Asp Ile Arg Thr Glu Glu Ala Ile
 675 680 685

Tyr Gln Cys Cys Asp Leu Asp Pro Gln Ala Arg Val Ala Ile Lys Ser
 690 695 700

Leu Thr Glu Arg Leu Tyr Val Gly Gly Pro Leu Thr Asn Ser Arg Gly
 705 710 715 720

Glu Asn Cys Gly Tyr Arg Arg Cys Arg Ala Ser Arg Val Leu Thr Thr
 725 730 735

Ser Cys Gly Asn Thr Leu Thr Arg Tyr Ile Lys Ala Arg Ala Ala Cys
 740 745 750

Arg Ala Ala Gly Leu Gln Asp Cys Thr Met Leu Val Cys Gly Asp Asp
 755 760 765

Leu Val Val Ile Cys Glu Ser Ala Gly Val Gln Glu Asp Ala Ala Ser
 770 775 780

Leu Arg Ala Phe Thr Glu Ala Met Thr Arg Tyr Ser Ala Pro Pro Gly
 785 790 795 800

Asp Pro Pro Gln Pro Glu Tyr Asp Leu Glu Leu Ile Thr Ser Cys Ser
 805 810 815

Ser Asn Val Ser Val Ala His Asp Gly Ala Gly Lys Arg Val Tyr Tyr
 820 825 830

Leu Thr Arg Asp Pro Thr Thr Pro Leu Ala Arg Ala Ala Trp Glu Thr
 835 840 845

Ala Arg His Thr Pro Val Asn Ser Trp Leu Gly Asn Ile Ile Met Phe
 850 855 860

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Ala Pro Thr Leu Trp Ala Arg Met Ile Leu Met Thr His Phe Phe Ser
865 870 875 880

Val Leu Ile Ala Arg Asp Gln Leu Glu Gln Ala Leu Asn Cys Glu Ile
885 890 895

Tyr Gly Ala Cys Tyr Ser Ile Glu Pro Leu Asp Leu Pro Pro Ile Ile
900 905 910

Gln Arg Leu His Gly Leu Ser Ala Phe Ser Leu His Ser Tyr Ser Pro
915 920 925

Gly Glu Ile Asn Arg Val Ala Ala Cys Leu Arg Lys Leu Gly Val Pro
930 935 940

Pro Leu Arg Ala Trp Arg His Arg Ala Trp Ser Val Arg Ala Arg Leu
945 950 955 960

Leu Ala Arg Gly Gly Lys Ala Ala Ile Cys Gly Lys Tyr Leu Phe Asn
965 970 975

Trp Ala Val Arg Thr Lys Leu Lys Leu Thr Pro Ile Thr Ala Ala Gly
980 985 990

Arg Leu Asp Leu Ser Gly Trp Phe Thr Ala Gly Tyr Ser Gly Gly Asp
995 1000 1005

Ile Tyr His Ser Val Ser His Ala Arg Pro Arg Trp Phe Trp Phe Cys
1010 1015 1020

Leu Leu Leu Leu Ala Ala Gly Val Gly Ile Tyr Leu Leu Pro Asn Arg
1025 1030 1035 1040

<210> SEQ ID NO 10
 <211> LENGTH: 226
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Hepatitis B virus S antigen (HBsAg) sequence

<400> SEQUENCE: 10

Met Glu Asn Ile Thr Ser Gly Phe Leu Gly Pro Leu Leu Val Leu Gln
1 5 10 15

Ala Gly Phe Phe Leu Leu Thr Arg Ile Leu Thr Ile Pro Gln Ser Leu
20 25 30

Asp Ser Trp Trp Thr Ser Leu Asn Phe Leu Gly Gly Thr Thr Val Cys
35 40 45

Leu Gly Gln Asn Ser Gln Ser Pro Thr Ser Asn His Ser Pro Thr Ser
50 55 60

Cys Pro Pro Thr Cys Pro Gly Tyr Arg Trp Met Cys Leu Arg Arg Phe
65 70 75 80

Ile Ile Phe Leu Phe Ile Leu Leu Leu Cys Leu Ile Phe Leu Leu Val
85 90 95

Leu Leu Asp Tyr Gln Gly Met Leu Pro Val Cys Pro Leu Ile Pro Gly
100 105 110

Ser Ser Thr Thr Ser Thr Gly Pro Cys Arg Thr Cys Met Thr Thr Ala
115 120 125

Gln Gly Thr Ser Met Tyr Pro Ser Cys Cys Cys Thr Lys Pro Ser Asp
130 135 140

Gly Asn Cys Thr Cys Ile Pro Ile Pro Ser Ser Trp Ala Phe Gly Lys
145 150 155 160

Phe Leu Trp Glu Trp Ala Ser Ala Arg Phe Ser Trp Leu Ser Leu Leu
165 170 175

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Val Pro Phe Val Gln Trp Phe Val Gly Leu Ser Pro Thr Val Trp Leu
 180 185 190

Ser Val Ile Trp Met Met Trp Tyr Trp Gly Pro Ser Leu Tyr Ser Ile
 195 200 205

Leu Ser Pro Phe Leu Pro Leu Leu Pro Ile Phe Phe Cys Leu Trp Val
 210 215 220

Tyr Ile
 225

<210> SEQ ID NO 11
 <211> LENGTH: 212
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Hepatitis B virus C antigen and e antigen
 (HBcAg/HBeAg) sequence

<400> SEQUENCE: 11

Met Gln Leu Phe His Leu Cys Leu Ile Ile Ser Cys Ser Cys Pro Thr
 1 5 10 15

Val Gln Ala Ser Lys Leu Cys Leu Gly Trp Leu Trp Gly Met Asp Ile
 20 25 30

Asp Pro Tyr Lys Glu Phe Gly Ala Thr Val Glu Leu Leu Ser Phe Leu
 35 40 45

Pro Ser Asp Phe Phe Pro Ser Val Arg Asp Leu Leu Asp Thr Ala Ser
 50 55 60

Ala Leu Tyr Arg Glu Ala Leu Glu Ser Pro Glu His Cys Ser Pro His
 65 70 75 80

His Thr Ala Leu Arg Gln Ala Ile Leu Cys Trp Gly Glu Leu Met Thr
 85 90 95

Leu Ala Thr Trp Val Gly Val Asn Leu Glu Asp Pro Ala Ser Arg Asp
 100 105 110

Leu Val Val Ser Tyr Val Asn Thr Asn Met Gly Leu Lys Phe Arg Gln
 115 120 125

Leu Leu Trp Phe His Ile Ser Cys Leu Thr Phe Gly Arg Glu Thr Val
 130 135 140

Ile Glu Tyr Leu Val Ser Phe Gly Val Trp Ile Arg Thr Pro Pro Ala
 145 150 155 160

Tyr Arg Pro Pro Asn Ala Pro Ile Leu Ser Thr Leu Pro Glu Thr Thr
 165 170 175

Val Val Arg Arg Arg Gly Arg Ser Pro Arg Arg Arg Thr Pro Ser Pro
 180 185 190

Arg Arg Arg Arg Ser Gln Ser Pro Arg Arg Arg Arg Ser Gln Ser Arg
 195 200 205

Glu Ser Gln Cys
 210

<210> SEQ ID NO 12
 <211> LENGTH: 2227
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Hepatitis A virus sequence

<400> SEQUENCE: 12

Met Asn Met Ser Lys Gln Gly Ile Phe Gln Thr Val Gly Ser Gly Leu

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1	5	10	15
Asp His Ile Leu Ser Leu Ala	Asp Ile Glu Glu Glu Gln Met Ile Gln		
20	25	30	
Ser Val Asp Arg Thr Ala Val Thr Gly Ala Ser Tyr Phe Thr Ser Val			
35	40	45	
Asp Gln Ser Ser Val His Thr Ala Glu Val Gly Ser His Gln Ile Glu			
50	55	60	
Pro Leu Lys Thr Ser Val Asp Lys Pro Gly Ser Lys Lys Thr Gln Gly			
65	70	75	80
Glu Lys Phe Phe Leu Ile His Ser Ala Asp Trp Leu Thr Thr His Ala			
85	90	95	
Leu Phe His Glu Val Ala Lys Leu Asp Val Val Lys Leu Leu Tyr Asn			
100	105	110	
Glu Gln Phe Ala Val Gln Gly Leu Leu Arg Tyr His Thr Tyr Ala Arg			
115	120	125	
Phe Gly Ile Glu Ile Gln Val Gln Ile Asn Pro Thr Pro Phe Gln Gln			
130	135	140	
Gly Gly Leu Ile Cys Ala Met Val Pro Gly Asp Gln Ser Tyr Gly Ser			
145	150	155	160
Ile Ala Ser Leu Thr Val Tyr Pro His Gly Leu Leu Asn Cys Asn Ile			
165	170	175	
Asn Asn Val Val Arg Ile Lys Val Pro Phe Ile Tyr Thr Arg Gly Ala			
180	185	190	
Tyr His Phe Lys Asp Pro Gln Tyr Pro Val Trp Glu Leu Thr Ile Arg			
195	200	205	
Val Trp Ser Glu Leu Asn Ile Gly Thr Gly Thr Ser Ala Tyr Thr Ser			
210	215	220	
Leu Asn Val Leu Ala Arg Phe Thr Asp Leu Glu Leu His Gly Leu Thr			
225	230	235	240
Pro Leu Ser Thr Gln Met Met Arg Asn Glu Phe Arg Val Ser Thr Thr			
245	250	255	
Glu Asn Val Val Asn Leu Ser Asn Tyr Glu Asp Ala Arg Ala Lys Met			
260	265	270	
Ser Phe Ala Leu Asp Gln Glu Asp Trp Lys Ser Asp Pro Ser Gln Gly			
275	280	285	
Gly Gly Ile Lys Ile Thr His Phe Thr Thr Trp Thr Ser Ile Pro Thr			
290	295	300	
Leu Ala Ala Gln Phe Pro Phe Asn Ala Ser Asp Ser Val Gly Gln Gln			
305	310	315	320
Ile Lys Val Ile Pro Val Asp Pro Tyr Phe Phe Gln Met Thr Asn Thr			
325	330	335	
Asn Pro Asp Gln Lys Cys Ile Thr Ala Leu Ala Ser Ile Cys Gln Met			
340	345	350	
Phe Cys Phe Trp Arg Gly Asp Leu Val Phe Asp Phe Gln Val Phe Pro			
355	360	365	
Thr Lys Tyr His Ser Gly Arg Leu Leu Phe Cys Phe Val Pro Gly Asn			
370	375	380	
Glu Leu Ile Asp Val Thr Gly Ile Thr Leu Lys Gln Ala Thr Thr Ala			
385	390	395	400
Pro Cys Ala Val Met Asp Ile Thr Gly Val Gln Ser Thr Leu Arg Phe			
405	410	415	

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Arg Val Pro Trp Ile Ser Asp Thr Pro Tyr Arg Val Asn Arg Tyr Thr
420 425 430

Lys Ser Ala His Gln Lys Gly Glu Tyr Thr Ala Ile Gly Lys Leu Ile
435 440 445

Val Tyr Cys Tyr Asn Arg Leu Thr Ser Pro Ser Asn Val Ala Ser His
450 455 460

Val Arg Val Asn Val Tyr Leu Ser Ala Ile Asn Leu Glu Cys Phe Ala
465 470 475 480

Pro Leu Tyr His Ala Met Asp Val Thr Thr Gln Val Gly Asp Asp Ser
485 490 495

Gly Gly Phe Ser Thr Thr Val Ser Thr Glu Gln Asn Val Pro Asp Pro
500 505 510

Gln Val Gly Ile Thr Thr Met Arg Asp Leu Lys Gly Lys Ala Asn Arg
515 520 525

Gly Lys Met Asp Val Ser Gly Val Gln Ala Pro Arg Gly Ser Tyr Gln
530 535 540

Gln Gln Leu Asn Asp Pro Val Leu Ala Lys Lys Val Pro Glu Thr Phe
545 550 555 560

Pro Glu Leu Lys Pro Gly Glu Ser Arg His Thr Ser Asp His Met Ser
565 570 575

Ile Tyr Lys Phe Met Gly Arg Ser His Phe Leu Cys Thr Phe Thr Phe
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Asn Ser Asn Asn Lys Glu Tyr Thr Phe Pro Ile Thr Leu Ser Ser Thr
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Ser Asn Pro Pro His Gly Leu Pro Ser Thr Leu Arg Trp Phe Phe Asn
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Leu Phe Gln Leu Tyr Arg Gly Pro Leu Asp Leu Thr Ile Ile Ile Thr
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Gly Ala Thr Asp Val Asp Gly Met Ala Trp Phe Thr Pro Val Gly Leu
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Lys Thr Ala Leu Gly Ala Val Arg Phe Asn Thr Arg Arg Thr Gly Asn
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Ile Gln Ile Arg Leu Pro Trp Tyr Ser Tyr Leu Tyr Ala Val Ser Gly
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Ala Leu Asp Gly Leu Gly Asp Lys Thr Asp Ser Thr Phe Gly Leu Phe
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Leu Phe Glu Ile Ala Asn Tyr Asn His Ser Asp Glu Tyr Leu Ser Phe
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Glu Glu Asp Arg Arg Phe Glu Ser His Ile Glu Cys Arg Lys Pro Tyr
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Lys Glu Leu Arg Leu Glu Val Gly Lys Gln Arg Leu Lys Tyr Ala Gln
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Arg	Arg	Phe	Gly	Phe	Ser	Leu	Ala	Ala	Gly	Arg	Ser	Val	Trp	Thr	Leu
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			885						890					895	
Glu	Lys	Trp	Thr	Glu	Met	Lys	Asp	Asp	Lys	Ile	Val	Ser	Leu	Ile	Glu
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Lys	Phe	Thr	Ser	Asn	Lys	Tyr	Trp	Ser	Lys	Val	Asn	Phe	Pro	His	Gly
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Met	Leu	Asp	Leu	Glu	Glu	Ile	Ala	Ala	Asn	Ser	Lys	Asp	Phe	Pro	Asn
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Lys Asp Tyr Glu Met Met Glu Phe Tyr Phe Asn Arg Gly Gly Thr Tyr 1570	1575	1580
Tyr Ser Ile Ser Ala Gly Asn Val Val Ile Gln Ser Leu Asp Val Gly 1585	1590	1595 1600
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Ser Lys Tyr Ser Leu Pro Ile Val Glu Glu Pro Glu Asp Tyr Lys Glu
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Asp Ala Ile Asn Met Asp Ser Ser Pro Gly Phe Pro Tyr Val Gln Glu
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Leu Gly Val His Pro Arg Leu Ala Gln Arg Ile Leu Phe Asn Thr Val
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Ile Asn Thr Ile Ile Tyr Ser Lys His Leu Leu Tyr Asn Cys Cys Tyr
2020 2025 2030

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<210> SEQ ID NO 15
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Hepatitis A virus sequence

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<400> SEQUENCE: 15

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tctttctgag gtttgtttat ttcttttgc cgctaact	7478

What is claimed is:

1. An improved vaccine composition that includes an antigen, wherein the improvement comprises ribavirin.

2. The improved vaccine composition of claim 1, wherein said antigen is a viral antigen.

3. The improved vaccine composition of claim 1, wherein said antigen is obtained from a virus selected from the group consisting of hepatitis A virus, hepatitis B virus, and hepatitis C virus.

4. The improved vaccine composition of claim 1, wherein said antigen is obtained from hepatitis C virus.

5. The improved vaccine composition of claim 1, wherein the amount of ribavirin is at least 0.25 mg.

6. The improved vaccine composition of claim 1, wherein the amount of ribavirin is between about 0.25 mg and 100 mg.

7. The improved vaccine composition of claim 1, wherein the amount of ribavirin is between about 0.25 mg and 25 mg.

8. The improved vaccine composition of claim 1, wherein the amount of ribavirin is between about 0.25 mg and 1 mg.

9. The improved vaccine composition of claim 1, wherein the amount of ribavirin is at least 0.1 mg ribavirin per kg body weight of a subject receiving said composition.

10. The improved vaccine composition of claim 1, wherein the amount of ribavirin is between about 0.1 mg ribavirin to about 1.0 mg ribavirin per kg body weight of a subject receiving said composition.

11. The improved vaccine composition of claim 1, wherein the amount of ribavirin is between about 1.1 mg ribavirin to about 2.0 mg ribavirin per kg body weight of a subject receiving said composition.

12. The improved vaccine composition of claim 1, wherein the amount of ribavirin is between about 2.1 mg ribavirin to about 3.0 mg ribavirin per kg body weight of a subject receiving said composition.

13. The improved vaccine composition of claim 1, wherein the amount of ribavirin is between about 3.1 mg ribavirin to about 4.0 mg ribavirin per kg body weight of a subject receiving said composition.

14. A method of making the improved vaccine composition of claim 1 comprising:

providing an antigen;

providing ribavirin; and

combining said antigen and said ribavirin so as to make said improved vaccine composition.

15. The method of claim 14, wherein said antigen is a viral antigen.

16. The method of claim 14, wherein said antigen is obtained from a virus selected from the group consisting of hepatitis A virus, hepatitis B virus, and hepatitis C virus.

17. The method of claim 14, wherein said antigen is obtained from hepatitis C virus.

18. The method of claim 14, wherein the amount of ribavirin is at least 0.25 mg.

19. The method of claim 14, wherein the amount of ribavirin is between about 0.25 mg and 100 mg.

20. The method of claim 14, wherein the amount of ribavirin is between about 0.25 mg and 25 mg.

21. The method of claim 14, wherein the amount of ribavirin is between about 0.25 mg and 1 mg.

22. The method of claim 14, wherein the amount of ribavirin is at least 0.1 mg ribavirin per kg body weight of a subject receiving said composition.

23. The method of claim 14, wherein the amount of ribavirin is between about 0.1 mg ribavirin to about 1.0 mg ribavirin per kg body weight of a subject receiving said composition.

24. The method of claim 14, wherein the amount of ribavirin is between about 1.1 mg ribavirin to about 2.0 mg ribavirin per kg body weight of a subject receiving said composition.

25. The method of claim 14, wherein the amount of ribavirin is between about 2.1 mg ribavirin to about 3.0 mg ribavirin per kg body weight of a subject receiving said composition.

26. The method of claim 14, wherein the amount of ribavirin is between about 3.1 mg ribavirin to about 4.0 mg ribavirin per kg body weight of a subject receiving said composition.

27. A method of enhancing an immune response to an antigen comprising:

providing a subject the improved vaccine composition of claim 1.

28. The method of claim 25, wherein said antigen is a viral antigen.

29. The method of claim 25, wherein said antigen is obtained from a virus selected from the group consisting of hepatitis A virus, hepatitis B virus, and hepatitis C virus.

30. The method of claim 26, wherein said antigen is obtained from hepatitis C virus.

31. An improved method of enhancing an immune response to an antigen that includes providing a subject an antigen, wherein the improvement comprises providing ribavirin.

32. The improved method of claim 31, wherein said antigen and said ribavirin are provided together.

33. The improved method of claim 31, wherein said antigen and ribavirin are provided separately.

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